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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/820,745	03/30/2001	Tom L. Blundell	620-139	4747

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 09/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/820,745	BLUNDELL ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *1-4,10,12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/15/01, 3/18/03 &12/22/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Group III, claims 5-9, in the reply filed on July 9, 2004 is acknowledged. The traversal is on the ground(s) that searching Groups I-III together would not place undue burden on the examiner. This is not found persuasive because searching the invention of Group I requires search in class 424, subclass 94.5 which is not required for Group III. In contrast, the invention of Group III requires search in Class 702, which is not required for Group I. As indicated in the prior Office action, June 9, 2004, the invention of Groups II and III are independent methods having different products and steps. As such, their search may overlap, but each method would require its own search in the patent and non-patent literature. Thus, there is a search burden to examine Groups I-III together in the same application. The examiner regrets any confusion caused by the inadvertent typographical error in the previous Office action. Group V clearly contains claims 12 and 13. As correctly pointed out by the applicants, claim 11 is drawn to a modeling method. As such, it defines a new invention. The invention of claim 11 is unrelated to the methods of Groups II and III because the three methods are independent methods having different steps and products. Since the original restriction did not contain the invention of claim 11 and examining claim 11 along with claims 5-9 of Group II would not constitute a search burden on the examiner, claim 11 would be examined with elected Group II. Finally, the crystallization method of Claim 3 is appropriately included in Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4, 10, and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions of Groups I, II, IV, and V, there being no allowable generic or linking claim.

Applicant must perfect their compliance with the sequence rules, 37 CFR 1.821(a)(1) and (a)(2). Specifically, Figure 5 discloses several amino acid sequences, which are found in the sequence listing, but the sequence identification numbers are omitted from the Figure and the Figure description on page 14 of the specification. Applicants must insert the sequence identification number in either the figure description or file a new figure containing the sequence identification numbers. In addition, applicants must insert the sequence identification number after each occurrence of KPHMT.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Crystal Structure of *Escherichia coli* Keto-pantoate Hydroxymethyltransferase.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The examiner has no comment on the drawing filed September 4, 2001 because he has access only to photocopies of the original Figures. The photocopies of the three dimensional structure are of poor quality, and in many cases, it is difficult to identify the features being shown.

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to a method of crystallizing Ketopantoate Hydroxymethyltransferase (KPHMT) from *E. coli* in the presence of ketopantolactone (the product of KPHMT-catalyzed reaction) having a specific sequence and produces a monoclinic crystal described on page 17, first paragraph. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all possible crystals comprising a complex of KPHMT and any potential inhibitor of its activity. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a method of identifying inhibitor for KPHMT wherein said method comprising a step involving the crystallization of a potential modulator bound to KPMHT from *E. coli* and obtain a suitable crystal for X-ray structural analysis. The specification provides guidance and examples in the form of an assay to crystallize KPMHT from *E. coli* bound to ketopantolactone suitable for structure determination by X-ray crystallography, see pages 14-17 of the specification. While molecular biological techniques and genetic manipulation to make sufficient quantities of KPMHT and synthetic organic and inorganic methods to make almost any organic or inorganic compounds are available and known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of protein complexes with a modulator is lacking. There are two methods for obtaining a crystal of an enzyme-inhibitor complex, which are known in the prior art. The first is to diffuse an inhibitor to an already formed crystal of the enzyme/protein. In many instances, the crystal disintegrates immediately. The second, and more preferred method is to attempt to crystallize the complex by mixing the inhibitor and the enzyme together and identify a crystallization conditions wherein a

crystal of the enzyme-inhibitor complex suitable for X-ray analysis is formed. Thus, searching for a method to obtain a crystal for said the complex suitable for X-ray analysis is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation required for the synthesis of a potential inhibitor/activator, and screen for a suitable crystallization conditions is enormous. Since routine experimentation in the art does not include synthesizing large number of potential inhibitor/activator and screening vast numbers of crystallization conditions where the expectation of obtaining the desired crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the crystallization conditions wherein a crystal suitable for X-ray determination can be obtained. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over the commercial availability of computers and various software packages such as RASMOL, see the specification the paragraph bridging page 12 and 13, an admitted prior art, in view Jones *et al.* [IDS reference: J. Baceriol. 1993, Vol. 175, pages 2125-2130].

Software packages such as GRAM, DUCK, AUTODUCK or RASMOL are commercially available. RASMOL, an admitted prior art in the specification, see the specification, in particular the paragraph bridging page 12 and 13, is capable fitting the structure of candidate compound to the structure of ketopantoate hydroxymethyl-transferase (KPHMT) as defined by the atomic coordinates in Table 1. The only difference between the commercially available computers and software packages is the atomic coordinates of Table 1.

Jones *et al.* teach a method for cloning and expression of KPHMT from *E. coli*, see the abstract. They teach both the nucleic acid encoding said KPHMT and the amino acid sequence encoded by said nucleic acid shown Figure 3. Also, they teach that pantothenic acid is a precursor to coenzyme A, and is synthesized by microorganisms and plant but not mammals, which require it as part of their diet. Finally, they teach that KPHMT catalyzes the first committed step in the biosynthesis of

pantothenic, which is the formation of ketopantoate from ketoisovalerate, see the first paragraph following the abstract.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over the fact that homology modeling methods are well known in the prior art, see the specification on page 11, lines 23-25, in view Kurtov *et al.* [IDS reference: Mol. Gene. Genet. 1999, Vol. 262, pages 115-120].

Homology modeling methods are well known in the prior art, which is an admitted prior art in the specification. The only difference between the admitted prior art and the claimed invention are the atomic coordinates.

Kurtove *et al.* teach that KPHMT is a target for development antifungal drugs because mammals do not have KPHMT, see abstract and the last four lines on page 115. They report the cloning of the gene encoding KPHMT from *Aspergillus nidulans*. Figure 2B show the nucleic acid encoding *A. nidulans* KPHMT as well as its amino acid sequence, which is 58% similar to that of *E. coli*, see page 118, left column, third paragraph.

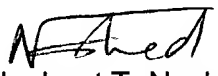
Kurtove *et al.* provide one of ordinary skill in the art with motivation to identify potential inhibitor for KPHMT as they teach that KPHMT is a target for developing antifungal agent. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to develop a method of identifying potential inhibitors for KPHMT, which would include a step of obtaining the molecular model for the *A. nidulans* KPHMT. The ordinary skill in the art would have relied on the well-known modeling methods to construct a molecular model for KPHMT and use the model to identify potential inhibitor for the enzyme by well-known methods in the art. As indicated above the only difference between the cited prior above and the claimed invention are the novel atomic coordinates. Data, which are fed into known algorithm whose purpose is to compare or modify those data using series of processing steps, do not impose a change in processing steps and are thus nonfunctional descriptive material. A method used for its known purpose to compare data sets does not become nonobvious merely because a new data becomes available for analysis. Nonfunctional descriptive material cannot render nonobvious an invention that has otherwise been obvious. See *In re Gulak*, 703 F2d 1381, 1385 (Fed. Cir. 1983). Atomic coordinates can't render a known method for modeling a structure of an enzymes non-obvious, claim 11.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1652